

REVIEW

Non-hormonal therapies for the treatment of menopausal symptoms

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ABSTRACT

Hot flushes affect approximately 75% of postmenopausal women and are one of the most distressing symptoms that women experience as they enter the menopause. The treatment of hot flushes is a common clinical challenge. Hormone replacement therapy (HRT) effectively reduces vasomotor symptoms by 80-90%, however, many patients may be unable or unwilling to undergo hormonal treatment. Publication of the results of the Women's Health Initiative (WHI) and the Million Women Study (MWS) has led to considerable uncertainties about the role of HRT among health professionals and women. The estrogen and progestin arm of the Women's Health Initiative and other recent reports suggest that HRT may increase the risk for coronary heart disease events, strokes, venous thromboembolism, and invasive breast cancer. Many expert groups recommend that combination hormonal therapy for the management of vasomotor symptoms should be limited to the shortest duration consistent with treatment goals and benefits versus risks for individual women. All of these concerns have generated interest in non-hormonal treatment of hot flushes. Such therapies, readily available for the menopausal patient could become a therapeutic nightmare -especially when taken without physician supervision. Data for these therapies are limited, and most of the studies have been conducted in women with a history of breast cancer. In this review we discuss the evidence underlying the commonly used non-hormonal therapies for hot flushes in terms of efficacy and safety.

Keywords: hot flushes, vasomotor symptoms, menopausal symptoms, complementary medicine, non-hormonal drugs.

INTRODUCTION

Hot flushes affect approximately 75% of postmenopausal women and are one of the most distressing symptoms that women experience as they enter the menopause. Symptoms typically begin a few years before natural menopause and usually continue for 1-5 years, although a small percentage of women may have symptoms for up to 15 years (1, 2). This population also appears to suffer from other symptoms related to the menopause, including depression, anxiety, easy fatigability and insomnia. In fact, this cluster of complaints may actually be related to the poor

sleep patterns associated with the intense night sweats of the hot flush symptom. Hot flushes also occur in women experiencing premature menopause due to bilateral oophorectomy or cytotoxic chemotherapy. This abrupt decline in estrogen often results in hot flushes that are more frequent and severe than those associated with natural menopause. In addition, 50% of postmenopausal women with breast cancer who are receiving tamoxifen experience hot flushes as an adverse effect of the drug (3).

Hormone replacement therapy effectively reduces vasomotor symptoms by 80-90% (4, 5), however, many patients may be unable or unwilling to

undergo hormonal treatment, e.g. patients with a history of endometrial cancer, venous thromboembolism, or breast cancer, or with a family history of breast cancer.

Publication of the results of the Women's Health Initiative (WHI) and the Million Women Study (MWS) has led to considerable uncertainties about the role of HRT among health professionals and women (6-20). The estrogen and progestin arm of the Women's Health Initiative (6) and other recent reports (21-23) suggest that hormone replacement therapy may increase the risk for coronary heart disease events, strokes, venous thromboembolism, and invasive breast cancer. Many expert groups recommend that combination hormonal therapy for the management of vasomotor symptoms should be limited to the shortest duration consistent with treatment goals and benefits versus risks for individual women (24, 25). All of these concerns have generated interest in non-hormonal treatment of hot flushes. As of 2001, forty-two percent of postmenopausal women in USA were using alternative therapies to treat menopausal symptoms (26). Such therapies, readily available for the menopausal patient could become a therapeutic nightmare -especially when taken without physician supervision.

Lifestyle Changes

As obesity and sedentary lifestyle are linked to increased hot flushes (27), women who need relief from mild hot flushes, should consider lifestyle changes first, these include:

1. *Environmental manipulations* to keep core body temperature as cool as possible observational studies have shown that lowering air temperature reduces hot flushes.
2. *Behavioral changes* as; a) aerobic sustained regular exercise (swimming, running), in observational studies, physically active women reported fewer and less severe hot flushes than an age-matched control group with sedentary lifestyles; significant decreases of more than 50% were noted (28). It is worth mentioning that high impact infrequent exercise can actually make hot flushes worse. b) avoiding hot flushes "triggers", c) paced respiration; in

three randomized, prospective clinical trials, paced respiration lowered hot flush frequency by approximately 50% more than the controls, a significant difference from baseline. d) lowering body mass index, and e) smoking cessation (29).

Clonidine

Clonidine is an α_2 -adrenergic agonist that reduces sympathetic outflow from the central nervous system and is indicated primarily for the treatment of hypertension. It has been hypothesized that since hot flushes may be associated with an excess of norepinephrine, clonidine may be useful in their treatment (30). Several studies have evaluated clonidine for the treatment of hot flushes; these studies have shown conflicting results, as well as questionable clinical significance.

In a multicenter, randomized, double-blind, placebo-controlled, crossover trial, oral clonidine was studied in 86 postmenopausal women with hot flushes. Patients were randomly assigned to receive clonidine 0.025 mg twice/day for 4 weeks followed by placebo for 4 weeks, or vice versa. Depending on the occurrence of hot flushes, the clonidine dosage could be titrated up to a maximum of 0.075 mg twice/day. A reduction in the mean number of hot flushes/week was greater in both groups during the clonidine treatment period compared with placebo (clonidine before placebo $p < 0.05$, placebo before clonidine $p < 0.001$). Frequency, severity, and duration of hot flushes were significantly improved with clonidine treatment when it was given as the first treatment compared with placebo. When patients received placebo first followed by clonidine, these improvements were still seen when compared with placebo; however, they did not reach statistical significance. It was also noted that women who experienced hot flushes for more than 1 year tended to have a greater placebo response than did women with hot flushes for less than 1 year. More than half the patients in both the placebo-first group and the clonidine-first group were receiving the maximum dosage of clonidine at the end of the treatment periods (31).

A double-blind, placebo-controlled, crossover trial

assessed clonidine 0.05 mg twice/day versus placebo in 66 postmenopausal women for 8 weeks. Postmenopausal women randomly assigned to receive clonidine experienced statistically significant reductions of 78%, 89%, and 88% in hot-flush frequency, severity, and duration, respectively, compared with the placebo group (32).

Another single-blind, placebo-controlled, dose-response study was conducted in 10 postmenopausal women with frequent hot flushes. In the six women who completed the trial, a dose-response relationship was observed. Increasing doses of clonidine were associated with significant reductions in hot flushes compared with baseline and placebo. The 0.4-mg dose produced a 46% mean reduction in hot flushes from baseline. No other information was given regarding the other clonidine strengths. Four patients withdrew from the study because of adverse effects from clonidine including severe fatigue, nausea, headaches, irritability, and dizziness (33).

The effect of clonidine 0.075 and 0.15 mg/day in 12 post-menopausal women with hypertension were studied in a randomized, double-blind, placebo-controlled, crossover trial. No significant effect was seen with the lower dosage of clonidine compared with placebo; however, both groups improved when compared with baseline hot-flush frequency. In the higher dosage arm, the clonidine 0.15 mg/day group and placebo group were associated with a significant reduction in hot flushes frequency compared with baseline measures, but not compared with each other. The effects of clonidine on blood pressure were not reported (34).

Three trials failed to find clonidine effective in reducing symptoms of hot flushes in postmenopausal women (35-37).

Two trials evaluated transdermal clonidine for the treatment of hot flushes in postmenopausal women. In a randomized, placebo-controlled, double-blind trial, 30 postmenopausal women were assigned to receive either transdermal clonidine 0.1 mg/24 hours or placebo for 8 weeks. Compared with baseline, clonidine significantly reduced hot-flush frequency, severity, and duration (38). Twelve (80%) of the 15 patients in the clonidine group reported a reduction in the frequency of hot flushes over baseline compared with five patients

in the placebo group ($p<0.04$). By the end of 8 weeks, hot flushes completely resolved in 4 of the 12 patients who reported improvements with clonidine, whereas the remaining 8 patients had a 60% or less reduction in the number of hot flushes. In the placebo group, significant reductions were noted in hot-flush frequency during weeks 5 ($p<0.05$), 6 ($p<0.05$), and 8 ($p<0.04$) only. In a more recent report the effect of transdermal clonidine 0.1 mg/24 hours was studied in 110 women receiving tamoxifen for breast cancer and experiencing hot flushes in a randomized double-blind crossover trial (39). Compared with placebo, clonidine was associated with a significantly greater reduction in hot-flush frequency by approximately 20% ($p<0.0001$) and severity by approximately 10% ($p=0.006$). An apparent placebo effect only on hot-flush frequency was noted during the first treatment period for both groups. During the second treatment phase, patients who crossed over to the placebo group reported a higher number of hot flushes and greater severity as compared with those of the first treatment period. When questioned about which patch worked best to reduce hot flushes, 48% of the patients selected the clonidine patch, 25% selected the placebo, and 27% could not tell a difference between the patches.

Oral clonidine was evaluated in a randomized, double-blind, placebo-controlled trial including 194 women with breast cancer suffering from tamoxifen-associated hot flushes. Compared with the placebo group, patients receiving clonidine reported a greater decrease in hot-flush frequency at week 4, 37% versus 20% (95% confidence interval [CI] 7-27%, $p=0.001$), and at week 8, 38% versus 24% (95% CI 3-27%, $p=0.006$). This translated to approximately 2.2 fewer hot flushes/day in the clonidine group. Hot-flush severity and duration also improved in the clonidine group; however, the percentage change compared with the placebo group was not statistically significant at weeks 4, 8, or 12. Significant improvement was seen in the quality-of-life scores for the clonidine group at weeks 4 and 8 compared with that of the placebo group; however, the median difference in all groups was zero. No difference was noted between the clonidine and placebo groups with regard to hot-

flush frequency, severity, and duration or quality-of-life scores at week 12 (40).

Clonidine side effects in published clinical trials were minimal and, for the most part, not significantly different from those when patients took placebo. The adverse effects included rash, nausea, gastrointestinal disturbances, sedation, and dry mouth and were associated with higher dosages of clonidine. However, one trial did find that difficulty sleeping was significantly higher in the clonidine group than in the placebo group ($p < 0.002$) (40). Clonidine patches were associated with a higher frequency of itching and erythema compared with the placebo patches. Blood pressure also was assessed during each of the trials, and no significant effect was noted. This is to be expected since the dosage of clonidine administered in the trials was lower than the dosage typically given for treating hypertension.

Although clonidine has been shown efficacious in reducing the frequency, duration, and severity of postmenopausal hot flushes, the results have been modest at the dosages administered in the trials. It may be useful in women with coexistent hypertension, although higher dosages would need to be given since the dosages administered in the trials did not show a significant effect on blood pressure. However, if higher dosages are given, patients may experience adverse effects associated with the clonidine therapy. It is also hard to determine what the optimal dosage and duration are for treatment of hot flushes and what long-term effects are associated with this treatment (41).

Selective serotonin and selective noradrenaline reuptake inhibitors (SSRIs / SNRI's)

Selective Serotonin Reuptake Inhibitors (SSRIs) are prescribed for different psychiatric conditions. The antidepressant, and anti-obsessive-compulsive effects of SSRIs are presumed to be due to their inhibition of central neuronal uptake of serotonin. Berendsen has proposed a hypothesis for the role of serotonin (5-hydroxytryptamine [5-HT]) in the initiation of hot flushes (42). In this model, estrogen withdrawal leads to a decreased serotonin blood level and an increased 5-HT_{2A} receptor sensitivity in the hypothalamus (involved in

thermoregulation). In response to stimuli (e.g., stress, caffeine), there is an increased release of 5-HT modulator, a protein. This leads to the blockade of 5-HT_{1B} receptors and a subsequent increased release of 5-HT. The increased serotonin stimulates the 5-HT_{2A} receptors in the hypothalamus, changing the set-point temperature. Autonomic reactions are triggered to cool the body, resulting in a hot flush. The use of SSRIs for the treatment of hot flushes is reasonable, based on this hypothesis. Several SSRIs have proven to be effective in clinical trials.

Paroxetine

Several studies examined the effectiveness of *Paroxetine*; An open-label trial of paroxetine was conducted in 30 survivors of breast cancer who experienced 14 or more hot flushes/week for at least 1 month (43). Patients completed daily diaries for 1 week while receiving no therapy and then received paroxetine 10 mg/day for 1 week followed by 4 weeks of paroxetine 20 mg/day. Twenty-seven women completed the 6-week study. The reductions in hot-flush frequency and severity scores were 67% and 75%, respectively. Statistically significant improvements were noted in depression, sleep, anxiety, and quality-of-life scores. Twenty-five (83%) of the 30 participants chose to continue paroxetine at the end of the study. The most common adverse effects associated with paroxetine were somnolence and dry mouth, which occurred in 60% and 43% of patients, respectively.

Weitzner et al reported their experience with paroxetine for the treatment of hot flushes and associated symptoms in 13 women with breast cancer (44). Patients received paroxetine 10 mg/night for 3 nights and then 20 mg/night. After 5 weeks of treatment, hot-flush ratings decreased in severity from a mean of 3.62 (hot flushes rated "quite a bit" or "extremely severe") to 2.08 (hot flushes rated "moderately severe"). At end point, 11 patients (85%) were still experiencing hot flushes, although the percentage of patients still rating their hot flushes as quite a bit or extremely severe had declined from 100% to 38% ($p = 0.008$). In addition, significant improvements were seen in general, emotional, and mental fatigue, as well as in the occurrence of clinical depression. The results

of these two pilot studies were limited by their uncontrolled design and small sample. In 2003, Stearns et al. published a large study to assess paroxetine for the treatment of hot flushes in 165 menopausal women (45). After a 1-week placebo run-in phase, this double-blind, placebo-controlled, parallel-group trial randomized women experiencing at least two to three hot flushes/day to receive paroxetine controlled release (CR) 12.5 mg/day, 25 mg/day, or placebo. Women must have discontinued any hormone replacement therapy at least 6 weeks before screening. Subjects with signs of active cancer or receiving chemotherapy or radiation therapy were excluded. Treatment with selective estrogen receptor modulators (e.g., tamoxifen) was permitted if therapy had been started at least 3 months before screening and the dosage remained unchanged throughout the study. At week 6, the mean placebo-adjusted reductions in hot-flush composite scores (frequency x severity) were -4.7 (95% CI -8.1 to -1.3, $p=0.007$) comparing paroxetine CR 12.5 mg/day with placebo and -3.6 (95% CI -6.8 to -0.4, $p=0.03$) comparing paroxetine CR 25 mg/day with placebo. This corresponded to median reductions of 62.2% in the 12.5-mg group and 64.6% in the 25-mg group versus 37.8% for the placebo group. By week 6, the median daily hot-flush frequency was reduced from 7.1 to 3.8 (mean reduction 3.3) in the paroxetine CR 12.5-mg group, from 6.4 to 3.2 (mean reduction 3.2) for the paroxetine CR 25-mg group, and from 6.6 to 4.8 (mean reduction 1.8) for the placebo group. The most frequently reported adverse events for paroxetine CR were headache, nausea, and insomnia, with fewer reports from patients in the paroxetine CR 12.5-mg group, and 89% of these events were mild or moderate in severity.

Fluoxetine

The efficacy of *Fluoxetine* for the treatment of hot flushes was evaluated in a placebo-controlled, double-blind, crossover trial (46). Eighty-one women with a history of breast cancer or a perceived increased risk of breast cancer were randomly assigned to receive fluoxetine 20 mg/day or placebo for 4 weeks. Subjects then crossed over to the alternative treatment arm for an additional 4 weeks. Women had at least 14 bothersome hot

flushes/week and were allowed to continue tamoxifen if they had been receiving therapy for at least 1 month and were planning to continue therapy for the duration of the study. Patients taking fluoxetine or other antidepressants for 2 years before study entry were excluded. Women reported occurrence of hot flushes in a diary for 1 week without study drug and during the 8-week study period. At baseline, 56% and 53% of patients in the placebo-to-fluoxetine and fluoxetine-to-placebo groups, respectively, were receiving concurrent tamoxifen, and the median hot-flush occurrence was 7 and 7.4, respectively. At the end of the first treatment period (4 wks), median hot-flush frequency decreased by 3.4 hot flushes/day (42%) in the fluoxetine group versus 2.5 hot flushes/day (31%) in the placebo group ($p=0.54$). Hot-flush scores decreased by 50% in the fluoxetine arm versus 36% in the placebo arm ($p=0.35$). Crossover analysis indicated that patients taking fluoxetine experienced a median improvement of 1.5 hot flushes/day (19%) and 3.1 hot-flush score units/day (24%) versus placebo ($p=0.01$ and 0.02 , respectively). No significant differences were noted in any of the checklist-determined toxicities (appetite loss, sleeplessness, nausea, dizziness, constipation, nervousness, mood changes, fatigue, and abnormal sweating) between the two study arms during the first randomized period. After the 9 weeks, when patients were still blinded to the study arm and asked which treatment period was more efficacious, 47% of patients thought the fluoxetine period was superior, 22% thought the placebo period was superior, and 31% could not tell ($p=0.14$). Fluoxetine resulted in a modest improvement in hot flushes. A recent prospective study, however, was unable to demonstrate any benefit for fluoxetine over a placebo in reducing hot flushes(47).

Citalopram

In a recent prospective, randomized, 9-month, placebo-controlled, double-blind study assessing Citalopram and fluoxetine in the treatment of postmenopausal symptoms one hundred fifty healthy women suffering from menopausal symptoms were recruited to this placebo-controlled double-blind study with a follow-up period of 9 months. They were randomized into three groups

receiving placebo, fluoxetine, or citalopram. The initial dose was 10 mg of both fluoxetine and citalopram, and it was increased to 20 mg at 1 month and to 30 mg at the 6-month visit. The main outcome measures were hot flushes and Kupperman index. There were no statistically significant differences between the groups in respect to number of hot flushes, Kupperman index, or Beck's depression scale, although there was a tendency in all these parameters in favor of SSRIs versus placebo. Insomnia improved significantly in the citalopram group versus placebo. Discontinuation rates at nine months were 40% in the placebo group, 34% in the fluoxetine group and 34% in the citalopram group. The study concluded that compared with placebo, citalopram and fluoxetine have little effect on hot flushes and cannot therefore be recommended for the treatment of menopausal symptoms, if vasomotor symptoms are the main complaint (47).

Sertraline

A randomized, double-blind, placebo-controlled, crossover study using 6 weeks of sertraline (50 mg each morning) versus placebo was conducted on 62 breast cancer survivors on adjuvant tamoxifen reporting bothersome hot flushes. Patients were asked to keep a daily hot flush diary to record hot flush frequency and severity, from which hot flush scores (frequency x severity) were calculated. Forty-seven women completed the first 6 weeks and 39 completed 12 weeks. The baseline daily hot flush frequency and score were 5.8 (standard deviation 4.1) and 11.5 (14.0), respectively. At the end of the first 6 weeks, hot flush frequency decreased by 50% in 36% of those taking sertraline compared to 27% taking placebo. In the crossover analysis, sertraline was significantly more effective than placebo: women crossing from placebo to sertraline had a decrease (-0.9 and -1.7) in hot flush frequency and score, whereas those crossing from sertraline to placebo had an increase (1.5 and 3.4) in hot flush frequency and score ($p = 0.03$ and 0.03). Forty-eight percent preferred the sertraline period, 11% preferred the placebo period, and 41% had no preference ($p = 0.006$). The authors concluded that sertraline decreases hot flushes in breast cancer survivors taking tamoxifen and that further study of sertraline for the management of

hot flushes is warranted (48).

Trazodone

Trazodone is a weak SSRI that is generally used for its antidepressant effects. Pansini et al. 1995 have observed the efficacy of oral trazodone (75 mg/day) in the treatment of the climacteric symptoms in 25 menopausal patients recruited at the Menopause Clinic of Ferrara University Hospital. The symptoms were scored from 0 to 3 according to presence and intensity. The patients were all complaining of climacteric neurovegetative symptoms (average symptom score 2.43). Symptoms scores were recorded before starting treatment and then again after 3 months. The intensity of hot flushes appeared reduced but was not statistically significant (49).

Venlafaxine

Venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and weak inhibitor of dopamine reuptake. Evidence suggests that the pharmacologic properties of the drug changes as the dosage is increased within the dosing range. Serotonin reuptake inhibition is present at both low and high dosages; however, the inhibition of norepinephrine reuptake occurs more profoundly at higher dosages, somewhere at or above 150 mg/day (50). While giving venlafaxine for other clinical conditions, an improvement in patients experiencing hot flushes was noticed. Based on these positive anecdotal experiences, several studies were conducted to evaluate the efficacy of venlafaxine for the treatment of hot flushes.

In a phase II evaluation of venlafaxine for the treatment of hot flushes (51), 28 women with a history of breast cancer or men undergoing androgen-deprivation therapy received oral venlafaxine 12.5 mg twice/day for 4 weeks. Before treatment, patients recorded the occurrence of hot flushes in a diary for 1 week to collect baseline data. Efficacy measures included the average number of daily hot flushes in 1 week, the weekly hot-flush score, the proportion of patients who thought the drug was helping them, and the proportion of patients who wanted to continue taking venlafaxine at the end of the trial. After 4 weeks, a greater than 50% reduction in hot-flush

scores compared with baseline was seen in 58% of patients who completed the study. Median weekly hot-flush scores were reduced by 55% from baseline. Overall, 68% of patients thought that venlafaxine helped reduce hot-flush activity and 64% wished to continue taking the drug after completion of the study. Venlafaxine appeared to be well tolerated and to result in an improvement in fatigue, dry mouth, sweating, trouble sleeping, and nervousness, although statistically significant improvements were seen only for fatigue and sweating.

A double-blind, placebo-controlled, randomized study compared placebo with three dosages of extended-release venlafaxine (37.5, 75, and 150 mg/day) in 191 women with a history of breast cancer or who were worried about taking estrogen for fear of breast cancer (52). Subjects were aged 18 years or older, experienced 14 or more troublesome hot flushes/week, and had hot flushes severe enough to desire therapeutic intervention. The primary end point was average daily hot-flush score calculated from daily hot-flush questionnaires. Patients were randomly assigned to one of four treatments: 37.5 mg/day for 28 days; 37.5 mg/day for 7 days, then 75 mg/day for 21 days; 37.5 mg/day for 7 days, 75 mg/day for 7 days, then 150 mg/day for 14 days; or placebo for 28 days. After week 4 of treatment, when each titration group had been taking the assigned maximum dosage for at least 2 weeks, the median hot-flush scores were reduced from baseline by 27%, 37%, 61%, and 61% in the placebo and the extended-release venlafaxine 37.5-, 75-, and 150-mg groups, respectively. Changes in hot-flush scores within an individual in groups assigned escalating dosages during the titration reflected a similar pattern in that there were significant decreases in hot-flush scores from baseline to 37.5 mg/day ($p=0.01$) and from 37.5 to 75 mg/day ($p=0.01$), but not when the dosage was increased from 75 to 150 mg/day ($p=0.74$). In addition, significant decreases in hot-flush scores occurred within the first week and reduction in hot-flush activity was unrelated to baseline depression. Overall quality-of-life score increased from baseline to week 4 by an average of three points in the three venlafaxine groups and decreased three points in the placebo group. Adverse effects

including decreased appetite, dry mouth, constipation, and nausea were dose related. Dry mouth occurred significantly more with all venlafaxine doses than with placebo ($p<0.05$), although the 150-mg dose caused significantly more dry mouth than did the two lower doses ($p=0.0006$ for 37.5 mg, $p=0.02$ for 75 mg). Decreased appetite and nausea both occurred significantly more with the 75- and 150-mg doses than with placebo ($p<0.05$); constipation was only significantly higher in the venlafaxine 150-mg group ($p<0.05$). This trial mainly studied women with breast cancer who were experiencing at least 14 hot flushes/week. Furthermore, 69% of patients in this trial were taking tamoxifen. Although stratification of patients according to tamoxifen therapy did not reveal any differences in hot-flush frequency, since only 30% of subjects in each group were not taking tamoxifen, the study had limited power to ensure that there was no tamoxifen effect. The short duration of this trial, urged further studies to determine if venlafaxine continues to alleviate hot flushes at long term.

An open-label continuation phase of the previously mentioned study by Loprinzi et al 1998, examined extended efficacy and toxicity data for 102 patients continuing with extended-release venlafaxine therapy (53). During this study, women could self-titrate the venlafaxine dosage anywhere from 37.5–150 mg/day for optimal effectiveness. The study demonstrated that the reduction in hot flushes reported in the randomized trial phase was maintained during the open-label study, and no additional benefits were seen with venlafaxine dosages higher than 75 mg/day. In addition, toxicity did not increase over time.

Whether these findings can be generalized to postmenopausal women without breast cancer or with less frequent hot flushes required further study. A recent study by Evans et al. was designed to evaluate the effectiveness of extended-release venlafaxine for treatment of postmenopausal hot flushes in a general population rather than women with a history of breast cancer and extended the treatment period to 12 weeks (54).

Eighty postmenopausal women with more than 14 hot flushes per week were randomized to receive treatment with extended-release venlafaxine or placebo. Participants received 37.5 mg daily for 1

week, followed by 75 mg daily for 11 weeks. Daily hot flush severity scores and adverse effects were recorded by subjects. Baseline and monthly follow-up questionnaires assessed patient-perceived hot flush score, quality of life, and sexual function. Participants were treated for 12 weeks.

Of the 80 subjects who enrolled in the study, 40 were in the treatment group and 40 in the control group. Of these, 61 completed the study. Subjective assessment at monthly visits of the effects of hot flush symptoms on daily living were significantly improved in the treatment group. Hot flush severity scores based on daily diaries were somewhat lower in the treatment group, but the between-group difference did not reach statistical significance. Three side effects, dry mouth, sleeplessness, and decreased appetite, were significantly more frequent in the venlafaxine group, but others, including dizziness, tremors, anxiety, diarrhea, and rash, were significantly less frequent. The effectiveness of treatment was further supported by the observation that 93% of subjects in the treatment group chose to continue treatment with venlafaxine after completion of the study. However, the estimated difference between the treatment and control groups in average diary-based weekly hot flush severity scores was only 2 points. This resulted from a reduction in frequency; there was no apparent reduction in severity of reported episodes. Although the upper confidence limit of 8.3 points for the between-group difference in the severity scores was consistent with a clinically meaningful effect, it may be that the patients' perceptions of the impact of their hot flushes on daily life was significantly improved by the treatment even though the reduction in the more direct measure of hot flush severity is relatively small. This difference may be due to the antidepressant effect of venlafaxine. It is possible that the improvement in the sense of well-being brought about by the venlafaxine altered the women's perceptions of their hot flushes.

There were several limitations of this study. There was no run-in period, and baseline data were not obtained before treatment for hot flush severity scores and daily adverse effects. Further, a larger sample size might have revealed a significant difference in hot flush severity scores.

Thus, this study indicated that extended-release

venlafaxine is an effective treatment option for postmenopausal hot flushes. Women perceived that the severity of their hot flushes, particularly their interference with daily activities, was significantly decreased with treatment. Although several adverse effects were noted in the venlafaxine group, most women (93%) continued treatment beyond the conclusion of the study, suggesting that the benefits of treatment outweighed the discomfort of the adverse effects.

Mirtazapine

The antidepressant mirtazapine has a dual mode of action. It is a noradrenergic and specific serotonergic antidepressant (NaSSA) that acts by antagonizing the adrenergic α_2 -autoreceptors and α_2 -heteroreceptors as well as by blocking 5-HT₂ and 5-HT₃ receptors. It enhances, therefore, the release of norepinephrine and 5-HT_{1A}-mediated serotonergic transmission. This dual mode of action may conceivably be responsible for mirtazapine's rapid onset of action. Dry mouth, sedation, and increases in appetite and body weight are the most common adverse effects.

After the early report by Waldinger et al., 2000 on the effectiveness of mirtazapine in reducing the severity of hot flushes and bouts of perspiration in four women (55), a prospective, single-arm, pilot clinical trial, developed to evaluate the efficacy and tolerability of mirtazapine for alleviating hot flushes. Twenty two patients' baseline characteristics were collected during the first week of the study. At the beginning of the second week, patients were started on mirtazapine at a dose of 7.5 mg at bedtime. The dose of mirtazapine was then increased to 15 mg at week 3 and to 30 mg at week 4. For week 5, patients could choose whether to take 15 mg/d or 30 mg/d. For the 16 patients who completed the study, the median reductions in total daily hot flushes and weekly hot-flush scores from their baselines were 52.5% and 59.5%, respectively. Although data from a double-blind, placebo-controlled clinical trial would be necessary to more definitively elucidate the efficacy and toxicity of mirtazapine in patients with hot flushes, the available data suggest that mirtazapine is a reasonable treatment to consider in patients with hot flushes, particularly in those with anxiety and sleep disturbances (56).

Gabapentin

The mechanism of action of gabapentin remains unclear, as it appears to have GABA-mimetic properties, although it does not bind to GABA receptors or influence the neural uptake of GABA. Gabapentin is used as an anticonvulsant and for the treatment of migraine headache and neuropathic pain. Six cases of successful treatment of hot flushes with gabapentin were reported by Guttuso (57). Dosages of gabapentin ranged from 200 mg at bedtime to 400 mg four times a day. The number of hot flushes per day reported by the patients decreased by 87 percent overall, with several patients experiencing resumption of hot flushes upon discontinuation of treatment. Patients responded in one to three days of therapy.

Loprinzi et al. also performed a pilot evaluation of gabapentin in the treatment of hot flushes in women with a history of breast cancer and women who wished not to take estrogen (58). Of the patients who completed four weeks of therapy with gabapentin, the mean reductions in hot flush frequency and severity were 66 percent and 70 percent, respectively. The dose of gabapentin used was 300 mg at bedtime for the first week, 300 mg twice a day during the second week, and 300 mg three times a day for the last two weeks. Fourteen of the 16 patients who completed the study chose to continue taking gabapentin. The authors concluded that gabapentin appears to be effective in the treatment of hot flushes, although the mechanism is unclear.

Another open-label pilot study was conducted in 19 women with breast cancer to investigate gabapentin's efficacy in reducing tamoxifen-induced hot flushes (59). Women received gabapentin 300 mg 3 times/day for 4 weeks. In the 14 women completing the study, the mean decrease in hot-flush duration was 70%, frequency 42%, and severity 50%. Ten women reported about 21% improvement in quality of life. The authors reported that the drug was well tolerated except for mild dizziness and drowsiness.

A randomized, double-blind, placebo-controlled trial was conducted in 59 postmenopausal women with seven or more hot flushes/day (60). Women were randomly assigned to 12 weeks of treatment with gabapentin 300-mg capsules 3 times/day or placebo. After 12 weeks, gabapentin resulted in a

45% decrease in mean hot-flush frequency and a 54% decrease in mean hot-flush composite score from baseline compared with a 29% and a 31% decrease, respectively, in the placebo group. These differences were statistically significant after the first week of treatment. In addition, 67% of gabapentin-treated patients experienced a 50% reduction in hot-flush composite score versus 38% of placebo-treated patients during week 12. At the end of the randomized trial, patients were given the option to enroll in a 5-week, open-label treatment phase during which all patients received gabapentin. Patients could increase the dosage to 2700 mg/day, if needed. Of the 50 patients who completed the open-label study, mean reductions in hot-flush frequency and composite scores were 54% and 61-67%, respectively, at week 17. In addition, 72% of patients experienced a greater than 50% reduction in hot-flush composite scores. Forty-four (81.5%) patients who started the open-label study requested to continue gabapentin after the open-label study ended. Of these patients, 25% requested a dosage of 900 mg/day or less, 61.4% requested a dosage of 900-1800 mg/day, and 13.6% requested a dosage of 1800-2700 mg/day. Patients requesting higher dosages tended to have a higher frequency of hot flushes at baseline. The most common adverse events during the double-blind study were somnolence (20%), dizziness (13.3%), and rash (6.7%), none of which occurred in the placebo group. Four patients (13.3%) in the gabapentin group and one (3%) in the placebo group withdrew because of adverse events. Higher gabapentin dosing during the open-label study was not associated with increased adverse events. This trial enrolled postmenopausal women, whereas previous trials included mostly women with a history of breast cancer, many of who were treated with tamoxifen.

Belladonna/ergotamine tartrate/phenobarbital combination (Bellergal, Bellamine)

The effect of Bellergal Retard (BR) on climacteric complaints was evaluated versus a placebo in an 8-wk double-blind study, followed by a 4-wk open study in which only BR was used as medication. There was a marked decrease in complaints in both

the BR and the placebo groups. Statistically significant differences were observed between the groups after 2 and 4 wk of treatment, indicating superior results with BR. After 8 wk of study however, these differences were no longer apparent (61). Recently, Turner et al., reported a case of a previously healthy, postmenopausal woman who developed anticonvulsant hypersensitivity syndrome while taking Bellamine S (belladonna alkaloids; ergotamine; phenobarbital) for hot flushes (62). Given their toxicity and unproven effectiveness, they are not recommended for the treatment of hot flushes.

Phytoestrogens

Phytoestrogens have no structural similarity to estrogen. They contain a phenolic ring that allows estrogen receptor binding, and their effect is 100 to 10,000 times weaker than actual estrogen. Indeed, depending on the tissue location and type, these phytoestrogens can act as estrogens or antiestrogens.

The role of phytoestrogens has stimulated considerable interest since populations consuming a diet high in isoflavones such as the Japanese appear to have lower rates of menopausal vasomotor symptoms, cardiovascular disease, osteoporosis; breast, colon, endometrial and ovarian cancers. However epidemiological studies need to be supported by data with analyses of the isoflavone content of foods and measures of their bioavailability (63). Phytoestrogens consists of three main groups: isoflavones, lignans, and coumestans.

Isoflavones (Soy)

Isoflavones are the most potent and this soy protein-based group has received the most attention. Several randomised controlled trials had been published comparing various preparations of soy with placebo. Only four out of the nine studies with a treatment phase lasting more than six weeks showed a significant improvement in symptoms compared to placebo. The most important of these trials includes a study of 102 women treated for 12 weeks which showed a 45% reduction in hot flushes in comparison to a 30% reduction in the

placebo group (64). In a recent trial of 75 postmenopausal women, a 61% reduction in symptom frequency and severity was demonstrated in the soy group compared to 21% in the placebo group (65).

Although mammographic density does not appear to be affected by soy preparations even after two year usage (66). However, patients with breast cancer or a family history of breast cancer should use concentrated isoflavones (and phytoestrogens as a whole) with caution. Long term treatment with soy has raised some concerns from the point of view of a low risk of endometrial hyperplasia (67), and clinicians should consider that soy can reduce the International Normalization Ratio (INR), thereby decreasing warfarin's effectiveness.

Lignans (Flaxseed)

An example of the lignan group of phytoestrogens is flaxseed (*Linum usitatissimum*). Flaxseed also contains omega-3 and omega-6 fatty acids and some researchers suggest that replacing dietary fats with flaxseed might be effective for patients with milder symptoms (68).

Coumestans (Red Clover)

Red clover (*Trifolium pretense*) belongs to the coumestins group. Five placebo-controlled studies evaluating the use of red clover isoflavones in the treatment of vasomotor symptoms have been conducted. Whilst the doses of red clover isoflavones (40-160 mg) and the duration of treatment (12-16 weeks) varied in these studies, all showed a numerical reduction in the number of hot flushes compared to placebo. However the differences only reached statistical significance in two out of the five studies (69-70). Despite the lack of statistical significance in three of the trials, including a relatively large study with over 100 patients recruited (71), a recent meta-analysis revealed a small reduction in the frequency of hot flushes in women receiving active treatment with red clover isoflavones (40-82mg/day) compared to those receiving placebo (72).

There were no serious safety concerns associated with short term administration of red clover isoflavones in any of these studies. Breast density does not appear to be adversely affected by red clover though long term randomized studies of breast cancer

incidence are lacking (73). Endometrial biopsy data are also lacking though ultrasound scans of endometrial thickness have been reassuring. This plant contains coumarins and could have an additive effect with warfarin therapy.

Black cohosh

Black cohosh (*cimicifuga racemosa*) has traditionally been used to treat a variety of conditions including rheumatism, rheumatoid arthritis, intercostal myalgia, sciatica, chorea, tinnitus, dysmenorrhoea, and uterine colic. Currently, black cohosh is the most popular herb for treatment of hot flushes. Its mechanism of action is unknown, it does not affect estrogenic receptors, nor does it have any stimulatory activity on uterine or breast tissue, more recent work suggests the effects may result from a central activity (74-76). Black cohosh is certified by the German Medicine's Control Agency for use in controlling menopausal symptoms for six months. A randomized study by Jacobson et al. 2001 involving 84 women with a history of breast cancer reported that black cohosh was similar to placebo in alleviating hot flushes (77). However, a previous study in which 80 menopausal women were randomized to receive estrogen, black cohosh, or placebo, the women receiving black cohosh had an 84 percent decrease in their hot flush symptoms compared with a 40 percent decrease in the estrogen and placebo groups (78). Results of a study involving 152 postmenopausal women receiving a high or a low dosage of black cohosh showed similar decreases in Kupperman index scores in the two groups at 12 weeks, suggesting that the higher dose was no more effective than the lower dose (79). Wuttke et al. reported a study in which 97 menopausal women were randomized to estrogen, black cohosh, or placebo showed black cohosh to be as effective as estrogen and superior to placebo in decreasing hot flush symptoms (80). In an open-label, randomized study involving 136 premenopausal women with a history of breast cancer who received black cohosh or placebo, researchers found that, at the end of the study, 46 percent of women receiving black cohosh were free of hot flushes ($P < .01$). Twenty-nine percent

of women receiving black cohosh continued to have severe hot flushes, compared with 74 percent of those receiving placebo (81).

A systematic review of the safety of black cohosh suggests there is a slight risk of minor, transient adverse events such as gastrointestinal upsets and rash if products are taken for a limited length of time at the recommended dose (82). There have been more serious adverse events reported, including hepatotoxicity; one case requiring liver transplantation. While it is not possible to confirm causality due to the limited evidence available, clinicians have been made aware of this potential serious adverse effect by the Medicines agency in the UK which recently reported seven cases (83). The ACOG stated that black cohosh may be helpful in the short-term (i.e., less than six months) treatment of women with vasomotor symptoms (84).

Ginseng

Ginseng is a perennial herb native to Korea and China, and has been extensively used in eastern Asia. A double-blind placebo controlled study including 384 menopausal women where the study group received 200mg per day of ginseng for four months failed to find any significant difference compared to placebo for reducing hot flushes, although parameters of well being and depression were improved (85). In addition to being known for causing postmenopausal bleeding in some patients, *panax ginseng* is a stimulant of breast cancer cells possibly via the same estrogenic effect noted on the uterus. Case reports have associated ginseng with postmenopausal bleeding and mastalgia. Further studies are required to confirm these effects, ginseng should not be recommended for menopausal symptom relief until more clinical studies are available (86).

Dong quai

Dong quai (*Angelica sinensis*) finds its roots in traditional Chinese medicine, where it is typically used in conjunction with other herbs. In a randomized trial 71 menopausal women were given 4.5gm per day of Dong quai for hot flushes,

there was no significant difference compared to placebo after six months of treatment (87). Interaction with warfarin and photosensitization have been reported due to the presence of coumarins. There is no evidence to support the use of Dong quai for vasomotor symptoms (88).

Evening primrose oil

Evening primrose oil (*Oenothera biennis*) is rich in gamma linolenic acid and has been used for menopausal symptom relief and its actions are most likely courtesy of the placebo effect. A placebo-controlled randomized trial concluded that gamma linolenic acid offers no benefit over placebo in treating menopausal flushing (89).

Wild yams

Wild yams (*Dioscorea villosa*), contain a compound known as diosgenin. Supporters of its use claim that diosgenin, applied as a cream, is changed in the body to progesterone and dehydroepiandrosterone (DHEA). While diosgenin can be converted to these compounds in vitro, it cannot be transformed in vivo. In a placebo-controlled study comprising 50 menopausal women topical application of wild yam twice daily showed no significant difference compared to placebo after six months (90).

St. John's wort

St. John's wort (*Hypericum perforatum*) has been shown to be efficacious in mild to moderate depression both in peri and premenopausal women due to its SSRI type effect, but its efficacy for vasomotor symptoms has not been proven (91). St John's wort is an inducer of the metabolic pathway of cytochrome P450 system and interacts with various drugs including warfarin, paroxetine, and the pill. In addition, anesthetologists have continued to have cases where patients had either inhibition or potentiation of anesthetics and sedative hypnotics when taking St John's wort. Currently, anesthetologists have consistently recommended a 3-week washout of St John's wort

before any operative procedure requiring anesthesia.

Kava kava

A Cochrane review concluded that it may be an effective symptomatic treatment option for anxiety but the data regarding menopausal symptoms are conflicting. There is some evidence for the use of kava, but safety concerns mean this herbal product is not a therapeutic option at present. Concern about liver damage has lead regulatory authorities to suspend or withdraw kava kava (92).

Ginkgo biloba

Use is widespread but there is little evidence to show that it improves menopausal symptoms. Some studies have shown a benefit for relief of anxiety and depression. There are claims for cognitive benefits from recent studies in postmenopausal women but these require confirmation from large long term studies (93).

Agnus Castus (Chasteberry)

Although there are some data for the benefits of agnus castus in premenstrual syndrome no such data exist for menopausal symptoms although occasionally used for this purpose (94).

Hops (*Humulus lupulus*)

A prospective, randomized, double-blind, placebo-controlled study over 12 weeks with 67 menopausal women, who were administered a hop extract (100 or 250µg). The responses were determined by means of a modified Kupperman index (KI) and a patients' questionnaire. All groups, including placebo, showed a significant reduction of the KI both after 6 weeks and after 12 weeks. The hop extract at 100µg was significantly superior to placebo after 6 weeks but not after 12 weeks. No dose-response relationship could be established, as the higher dose (250µg)

was less active than the lower dose both after 6 weeks and after 12 weeks (95).

Others

Alfalfa (*Medicago sativa*), Liquorice and Valerian root are also popular but there is no good evidence that they have any effect on menopausal symptoms (96).

Vitamin E

Vitamin E has shown some effectiveness in relieving hot flushes in breast cancer survivors. At 800 IU/day, it was slightly more effective than placebo, decreasing the hot-flush frequency, on average, by one hot flush per person per day (97). There is no evidence that vitamin E helps vasomotor symptoms in post-menopausal patients. However a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality has been published recently and revealed an increase in all-cause mortality with doses greater than or equal to 400IU per day (98).

Homeopathy

Clover & Ratsey in 2002 reported an uncontrolled, pilot outcome study, conducted at the Tunbridge Wells Homeopathic Hospital (TWHH) in 1998-1999. The study was conducted in out-patient consultations booked in the usual way. Thirty-one patients referred to the Department for menopausal flushes and seen for an initial consultation and at least one follow-up review, were assessed in three groups: Hot flushes: No history of carcinoma of the breast. Hot flushes: Treatment for breast carcinoma, not receiving Tamoxifen. Hot flushes: Treatment for breast cancer including Tamoxifen. For all patients, the initial and follow-up assessments included review of hot flush frequency and severity. Patients also completed their own self-assessment rating after follow-up consultations. The results indicated useful symptomatic benefit for all three groups of patients (99). This report was followed by a prospective observational study on homeopathic approach to the treatment of symptoms of oestrogen withdrawal in breast cancer patients. The active

intervention was an individualized homeopathic medicine. Forty women (89%) completed the study. Significant improvements in mean symptom scores were seen over the study period and for the primary end-point 'the effect on daily living' scores. Symptoms other than HF such as fatigue and mood disturbance appear to be helped. Significant improvements in anxiety, depression and quality of life were demonstrated over the study period. The homeopathic approach appeared to be clinically useful in the management of oestrogen withdrawal symptoms in women with breast cancer whether on or off tamoxifen and improves mood disturbance (100). These results were not supported by a recent randomized, double-blinded, placebo-controlled trial that was carried to evaluate the effectiveness of two types of homeopathy for the treatment of menopausal symptoms in breast cancer survivors (101).

Acupuncture

Several randomised controlled trials have shown that acupuncture reduces menopausal symptoms in patients experiencing the normal climacteric. It may have this effect by raising serotonin levels which alter the temperature set point in the hypothalamus (102). A small randomized controlled trial of 45 postmenopausal women undergoing shallow acupuncture, electro-acupuncture or oral estrogen administration showed a significant reduction in hot flush frequency in all three groups. The degree of symptom reduction was greatest in the estrogen group (103). A recent study on acupuncture and self acupuncture for long-term treatment of vasomotor symptoms in cancer patients, showed that acupuncture including self acupuncture is associated with long-term relief of vasomotor symptoms in cancer patients (104). Although no adverse effects were demonstrated in this study, adverse effects such as cardiac tamponade, pneumothorax and hepatitis have been described with acupuncture.

Reflexology

Reflexology aims to relieve stress or treat health conditions through the application of pressure to

specific points or areas of the feet. While it has been used for various conditions such as pain, anxiety and premenstrual syndrome there have been few studies for menopausal complaints. One randomized trial has been published so far where 67 women with vasomotor symptoms aged 45-60 years were randomized to receive reflexology or non specific foot massage. There was a reduction in symptoms in both groups but there was no significant difference between the groups (105).

Hypnotherapy

Hypnosis is a mind-body intervention that may be of significant benefit in treatment of hot flushes and other benefits may include reduced anxiety and improved sleep. Further, hypnosis may be a preferred treatment because of the few side-effects. Although some case studies showed that hypnotherapy appears to be a feasible and promising intervention for hot flushes, however this intervention has not been adequately studied (106, 107).

Other complementary therapies

Other complementary therapies include Alexander technique, Ayurveda, osteopathy, and Reiki. Further research is needed to understand their possible effects.

CONCLUSION

Hot flushes can significantly impact a woman's quality of life. Several nonhormonal therapies have shown positive results for the treatment of hot flushes. Although the efficacy of these therapies appears to be lower than traditional HRT, they have expanded the options for clinicians treating patients with a contraindication to hormonal therapy or for those patients unwilling to take hormones. The clinical goal is to tailor therapy to each individual woman's needs using the various options. Clinicians are advised to enlist women's participation in decision making when weighing the benefits, harms, and scientific uncertainties of nonhormonal therapies.

REFERENCES

1. Bachman GA. Vasomotor flushes in menopausal women. *Am J Obstet Gynecol* 1999;180:S312-16.
2. Berg G, Gottvall T, Hammar M, Lindgren R. Climacteric symptoms among women aged 60-62 in Linköping, Sweden, in 1986. *Maturitas* 1988;10:193-9.
3. Love RR, Cameron L, Connell BL, Leventhal H. Symptoms associated with tamoxifen treatment in postmenopausal women. *Arch Intern Med* 1991;151:1842-7.
4. Notelovitz M, Lenihan JP, McDermott M, Kerber IJ, Nanavati N, Arce J. Initial 17 β -estradiol dose for treating vasomotor symptoms. *Obstet Gynecol* 2000;95:726-31.
5. McNagny SE. Prescribing hormone replacement therapy for menopausal symptoms. *Ann Intern Med* 1999;131:605-16.
6. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321-33.
7. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003; 348:1839-54.
8. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* 2003; 289:2673-84.
9. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; 289:2651-62.
10. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: The Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; 289:2663-72.
11. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. The Women's Health Initiative randomized trial. *JAMA* 2003; 289: 3243-53.
12. Manson JE, Hsia J, Johnson KC, et al. Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; 349: 523-34.
13. Anderson GL, Judd HL, Kaunitz AM, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA* 2003; 290: 1739-48.
14. Cushman M, Kuller LH, Prentice R, et al; Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004; 292: 1573-80.
15. Barnabei VM, Cochrane BB, Aragaki AK, et al. Menopausal symptoms and treatment-related effects of estrogen and progestin in the Women's Health Initiative. *Obstet Gynecol* 2005; 105: 1063-73.

16. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291: 1701-1712.
17. Espeland MA, Rapp SR, Shumaker SA, et al; Women's Health Initiative Memory Study. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; 291: 2959-68.
18. Shumaker SA, Legault C, Kuller L, et al; Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; 291: 2947-58.
19. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419-427.
20. Beral V, Bull D, Reeves G; Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2005; 365: 1543-51.
21. Hulley S, Grady D, Bush T, et al, for the Heart and Estrogen/ Progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-13.
22. Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy: heart and estrogen/progestin replacement study follow-up (HERS II). *JAMA* 2002;288: 49-57.
23. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001;345:1243-9.
24. North American Menopause Society. Amended report from the NAMS advisory panel on postmenopausal hormone therapy. *Menopause* 2003;10:6-12.
25. Kirschstein R. Menopausal hormone therapy: summary of a scientific workshop. *Ann Intern Med* 2003;138:361-4.
26. Gass, MG, Taylor MD. Alternatives for women through menopause. *American Journal of obstetrics and Gynecology*.2001;185:(2 Suppl):S47-5.
27. The North American Menopause Society. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause* 2004 Jan-Feb;11(1):11-33.
28. Lindh-Astrand L, Nedstrand E, Wyon Y, Hammar M. Vasomotor symptoms and quality of life in previously sedentary postmenopausal women randomised to physical activity or estrogen therapy. *Maturitas* 2004; 48:97-105.
29. Ivarsson T, Spetz AC, Hammar M. Physical exercise and vasomotor symptoms in postmenopausal women. *Maturitas* 1998; 29:139-146.
30. Freedman RR. Biochemical, metabolic, and vascular mechanisms in menopausal hot flashes. *Fertil Steril* 1998;70:322-7.
31. Clayden JR, Bell JW, Pollard P. Menopausal flushing: a double-blind trial of a non-hormonal medication. *Br Med J* 1974;1:409-12.
32. Edington RF, Chagnon JP, Steinberg WM. Clonidine (Dixarit) for menopausal flushing. *Can Med Assoc J* 1980;123:23-6.
33. Laufer LR, Erlik Y, Meldrum DR, et al. Effect of clonidine on hot flashes in postmenopausal women. *Obstet Gynecol* 1982;60:583-6.
34. Bolli P, Simpson FO. Clonidine in menopausal flushing: a double-blind trial. *N Z Med J* 1986;144:369-70.
35. Lindsay R, Hart DM. Failure of response of menopausal vasomotor symptoms to clonidine. *Maturitas* 1978;1:21-5.
36. Wren BG, Brown LB. A double-blind trial with clonidine and a placebo to treat hot flushes. *Med J Aust* 1986;144:369-70.
37. Salmi T, Punnonen R. Clonidine in the treatment of menopausal symptoms. *Int J Gynaecol* 1982;60:583-6.
38. Nagamani M, Kelder ME, Smith ER. Treatment of menopausal hot flashes with transdermal administration of clonidine. *Am J Obstet Gynecol* 1987;156:561-5.
39. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12:155-8.
40. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center community oncology program study. *Ann Intern Med* 2000;132:788-93.
41. Loprinzi CL, Stearns V, Barton D. Centrally active nonhormonal hot flash therapies. *Am J Med*. 2005 Dec 19;118(12 Suppl 2):118-23.
42. Berendsen HH. The role of serotonin in hot flushes. *Maturitas* 2000;36:155-64.
43. Stearns V, Isaacs C, Rowland J, et al. A pilot trial assessing the efficacy of paroxetine (Paxil) in controlling hot flashes in breast cancer survivors. *Ann Oncol* 2000;11:17-22.
44. Weitzner MA, Moncello J, Jacobsen PB, Minton S. A pilot trial of paroxetine for the treatment of hot flashes and associated symptoms in women with breast cancer. *J Pain Symptom Manage* 2002;23:337-45.
45. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes. *JAMA* 2003;289:2827-34.
46. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002; 1578-83.
47. Suvanto-Luukkonen E., Koivunen R., Sundstrom H., Bloigu R., Karjalainen E., Haiva-Mallinen L., and Tapanainen JS. Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. *Menopause* 2005;12(1):18-26.
48. Kimmick, Gretchen G., Lovato, James, McQuellon, Richard, Robinson, Emily, and Muss, Hyman B. Randomized, Double-Blind, Placebo-Controlled, Crossover Study of Sertraline (Zoloft) for the Treatment of Hot Flashes in Women with Early Stage Breast Cancer Taking Tamoxifen. *Breast Journal* 2006; 12(2):114-122.
49. Pansini F, Albertazzi P, Bonaccorsi G, Zanotti L, Porto S, Dossi L, Campobasso C, Mollica G. Trazodone: a non-

- hormonal alternative for neurovegetative climacteric symptoms. *Clin Exp Obstet Gynecol*. 1995;22(4):341-4.
50. Horst DW, Preskorn SH. Mechanisms of action and clinical characteristics of three atypical antidepressants: venlafaxine, nefazodone, bupropion. *J Affect Disord* 1998;51:237-54.
 51. Loprinzi CL, Pisansky TM, Fonseca R, et al. Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. *J Clin Oncol* 1998;16:2377-81.
 52. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomized controlled trial. *Lancet* 2000;356:2059-63.
 53. Barton D, LaVasseur B, Loprinzi C, Novotny P, Wilwerding M, Sloan J. Venlafaxine for the control of hot flashes: results of a longitudinal continuation study. *Oncol Nurs Forum* 2002;29:33-40.
 54. Evans M. L., Pritts E. , Vittinghoff E., McClish K., Morgan K. S., and Jaffe R. B. Management of Postmenopausal Hot Flashes With Venlafaxine Hydrochloride: A Randomized, Controlled Trial. *Obstet. & Gynecol*. 2005;105:161-166
 55. Waldinger MD, Berendsen HH, Schweitzer DH. Treatment of hot flushes with mirtazapine: four case reports. *Maturitas*. 2000 Oct 31;36(3):165-8.
 56. Perez DG, Loprinzi CL, Barton DL, Pockaj BA, Sloan J, Novotny PJ, Christensen BJ. Pilot evaluation of mirtazapine for the treatment of hot flashes. *J Support Oncol*. 2004 Jan-Feb;2(1):50-6.
 57. Guttuso TJ. Gabapentin's effects on hot flashes and hypothermia. *Neurology*. 2000;54:21: 61-3
 58. Loprinzi CL, Barton DL, et al. Pilot evaluation of gabapentin for treating hot flashes. *Mayo Clin Proc*. 2002;77:1:159-1163
 59. Thummala AR, Griggs J, Rosenblatt J, et al. Pilot study using gabapentin on tamoxifen-induced hot flashes in women with breast cancer [abstr]. *Proc Am Soc Clin Oncol* 2002;21:362a.
 60. Guttuso T, Kurlan R, McDermott MP, Kiebertz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. *Obstet Gynecol* 2003;101: 337-45.
 61. Bergmans MG, Merkus JM, Corbey RS, Schellekens LA, Ubachs JM. Effect of Bellergeral Retard on climacteric complaints: a double-blind, placebo-controlled study. *Maturitas* 1987;9:227-34.
 62. Turner RB, Kim CC, Streams BN, Culpepper K, Haynes HA. Anticonvulsant hypersensitivity syndrome associated with Bellamine S, a therapy for menopausal symptoms. *J Am Acad Dermatol*. 2004 May;50(5 Suppl):S86-9.
 63. Glazier MG, Bowman MA. A review of the evidence for the use of phytoestrogens as a replacement for traditional estrogen replacement therapy. *Arch Intern Med*. 2001; 161:1161-72.
 64. Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E., Aloysio D The effect of dietary soy supplementation on hot flashes. *Obstet Gynecol* 1998; 91(1): 6-11.
 65. Faure ED, Chantre P, Mares P. Effects of a standardized soy extract on hot flashes: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 2002; 9(5): 329-34.
 66. Huntley AL and Ernst E. Soy for the treatment of perimenopausal symptoms – a systematic review. *Maturitas* 2004; 47:1-9.
 67. Unfer V, Casini ML, Castabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. *Fertil Steril* 2004; 82:145-148.
 68. Haggans C., Hutchins AM, Olson BA, et al. Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women. *Nutr Cancer*. 1999;33:188-95.
 69. Van de Weijer P and Barentsen R. Isoflavones from red clover (Promensil) significantly reduce menopausal hot flush symptoms compared with placebo. *Maturitas* 2002; 42:187-93.
 70. Jeri A. The Use of an Isoflavone Supplement to Relieve Hot Flushes. *The Female Patient* 2002; Baber R, Templeman C, Moreton T, Kelly G, and West L. Randomized placebo-controlled trial of an isoflavone supplement and menopausal symptoms in women. *Climacteric* 1999; 2:85-92.
 71. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen Supplements for the Treatment of Hot Flashes: The Isoflavone Clover Extract (ICE) Study. *JAMA* 2003; 290(2):207-214.
 72. Thompson Coon J, Pittler MH, Ernst E. Effectiveness of *Trifolium pratense* (red clover) isoflavones for menopause symptoms and women's health: systematic review and meta-analysis. *Submitted Canadian Journal of Medicine* 2004.
 73. Atkinson C, et al. Red clover-derived isoflavones and mammographic breast density: a double-blind, randomized, placebo-controlled trial. *Breast Cancer Research* 2004; 6(3):R170-179.
 74. Bodinet C, Freudenstein J. Influence of marketed herbal menopause preparations on MCF-7 cell proliferation. *Menopause* 2004;11:281-9.
 75. Burdette JE, Liu J, Chen SN, Fabricant DS, Piersen CE, Barker EL, et al. Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J Agric Food Chem* 2003;51:5661-70.
 76. Borrelli F, Ernst E. *Cimicifuga racemosa*: a systematic review of its clinical efficacy. *Eur J Clin Pharmacol* 2002;58:235-41.
 77. Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol* 2001;19:2739-45.
 78. Stoll W. *PhytoPharmacon* influences atrophic vaginal epithelium: double blind study-cimicifuga vs estrogenic substances. *Therapeuticon* 1987;1:23-31.
 79. Liske E, Hanggi W, Henneicke-von Zepelin HH, Boblitz N, Wustenberg P, Rahlfs VW. Physiological investigation of a unique extract of black cohosh (*Cimicifuga racemosa* rhizome): a 6-month clinical study demonstrates no systemic estrogenic effect. *J Womens Health Gend Based Med* 2002;11:163-74
 80. Wuttke W, Seidlova-Wuttke D, Gorkow C. The *Cimicifuga* preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers.

- Maturitas 2003;44(suppl 1):S67-S77.
81. Hernandez Munoz G, Pluchino S. Cimicifuga racemosa for the treatment of hot flushes in women surviving breast cancer. *Maturitas* 2003;44(suppl 1):S59-S65.
 82. Huntley A and Ernst E. A systematic review of the safety of black cohosh. *Menopause*. 2003 Jan-Feb; 10(1):58-64.
 83. Medical and Healthcare Product Regulatory Agency, Committee on Safety of Medicines. Black cohosh (cimicifuga racemosa) and hepatotoxicity. *The Current Problems in Pharmacovigilance* 2004;Oct:10.
 84. American College of Obstetricians and Gynecologists Committee on Practice Bulletins. Use of botanicals for management of menopausal symptoms. *Obstet Gynecol* 2001;97(suppl 1-11).
 85. Wiklund IK, Mattsson LA, Lindgren R, Limoni C. Effects of standardized ginseng extract on quality of life and physiological parameters in symptomatic postmenopausal women: a double-blind, placebo-controlled trial. *Swedish Alternative Medicine Group. Int J Clin Pharmacol Res* 1999;19:89-99
 86. Gass, MG, Taylor MD. Alternatives for women through menopause. *Am J Obstet Gynecol*.2001;185:(2 Suppl):S47-56.
 87. Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. *Fertil Steril* 1997;68:981-6.
 88. Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. *Menopause*. 2002;9:145-50.
 89. Chenoy R, Hussain S, Tayob Y, O'Brien PM, Moss MY, Morse PF. Effect of oral gamolenic acid from evening primrose oil on menopausal flushing. *BMJ* 1994;308:501-3.
 90. Komesaroff PA, Black CV, Cable V, Sudhir K. Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. *Climacteric* 2001;4:144-50.
 91. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's Wort for depression--an overview and meta-analysis of randomised clinical trials. *BMJ* 1996; 313(7052):253-8.
 92. Huntley AL, Ernst E. A systematic review of herbal medicinal products for the treatment of menopausal symptoms. *Menopause*. 2003 Sep-Oct;10(5):465-76.
 93. Elsabagh S, Hartley DE, File SE. Limited cognitive benefits in Stage +2 postmenopausal women after six weeks of treatment with Ginkgo biloba. *J Psychopharmacol* 2005; 19(2): 173-181.
 94. Roemheld-Hamm B. Chasteberry. *Am Fam Physician*. 2005 Sep 1;72(5):821-4.
 95. Heyerick A, Vervarcke S, Depypere H, Bracke M, Keukeleire DD. A first prospective, randomized, double-blind, placebo-controlled study on the use of a standardized hop extract to alleviate menopausal discomforts. *Maturitas*. 2005 Nov 28;
 96. Newton KM, Reed SD, Grothaus L, Ehrlich K, Guiltinan J, Ludman E, Lacroix AZ. The Herbal Alternatives for Menopause (HALT) Study: background and study design. *Maturitas*. 2005 Oct 16;52(2):134-46.
 97. Barton DL, Loprinzi CL, Quella SK, Sloan JA, Veeder MH, Egner JR, Fidler P, Stella PJ, Swan DK, Vaught NL, Novotny P. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998; 16(2):495-500.
 98. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Metaanalysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 2005; 142(1): 37-46.
 99. Clover A, Ratsey D. Homeopathic treatment of hot flashes: a pilot study. *Homeopathy*. 2002 Apr;91(2):75-9.
 100. Thompson EA, Reilly D. The homeopathic approach to the treatment of symptoms of oestrogen withdrawal in breast cancer patients. A prospective observational study. *Homeopathy*. 2003 Jul;92(3):131-4.
 101. Jacobs J, Herman P, Heron K, Olsen S, Vaughters L. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary randomized controlled trial. *J Altern Complement Med*. 2005 Feb;11(1):21-7.
 102. Nedstrand E, Wijma K, Wyon Y, Hammar M. Vasomotor symptoms decrease in women with breast cancer randomized to treatment with applied relaxation or electro-acupuncture: a preliminary study. *Climacteric*. 2005 Sep;8(3):243-50.
 103. Wyon Y, Wijma K, Nedstrand E, Hammar M. A comparison of acupuncture and oral estradiol treatment of vasomotor symptoms in postmenopausal women. *Climacteric*. 2004 Jun;7(2):153-64.
 104. Filshie J, Bolton T, Browne D, Ashley S. Acupuncture and self acupuncture for long-term treatment of vasomotor symptoms in cancer patients--audit and treatment algorithm. *Acupunct Med*. 2005 Dec;23(4):171-80.
 105. Williamson J, White A, Hart A, Ernst E. Randomised controlled trial of reflexology for menopausal symptoms. *BJOG* 2002; 109(9): 1050-1055.
 106. Younus J, Simpson I, Collins A, Wang X. Mind control of menopause. *Womens Health Issues*. 2003 Mar-Apr;13(2):74-8.
 107. Elkins G, Marcus J, Palamara L, Stearns V. Can hypnosis reduce hot flashes in breast cancer survivors? A literature review. *Am J Clin Hypn*. 2004 Jul;47(1):29-42.

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